THE EFFECTS OF DOPAMINE ANTAGONISTS ON THE DEVELOPMENT OF BEHAVIORAL SENSITIZATION TO COCAINE

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Morehead State University, 1998

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ABSTRACT

Recent research suggests that the development of behavioral sensitization to cocaine may be mediated by the repeated stimulation of either D1-type or D2-type dopamine receptors. The purpose of the present study was to test this hypothesis by determining whether concurrent treatments with a D1-type dopamine antagonist (SCH 23390) and a D2-type dopamine antagonist (eticlopride) combined would prevent the development of behavioral sensitization to cocaine.

Forty-eight male Wistar rats, that weighed between 200 and 250g were injected daily for four days with one of the following drug combinations: vehicle/vehicle, vehicle/cocaine (15mg/kg), SCH 23390 (0.1mg/kg)/eticlopride (0.1mg/kg)/vehicle, or SCH 23390/eticlopride/cocaine. Each rat was first injected S.C. with either a combination of SCH 23390 and eticlopride or vehicle, and then 25 min later, each rat was injected I.P. with either cocaine or vehicle. Five min after the second injection, each rat was tested for locomotor activity in photocell activity boxes (Med-Associates) for 60 min. On day five, all rats were tested for activity after a challenge injection of cocaine (10 mg/kg) alone.

The major findings were as follows: a) rats treated with cocaine alone were significantly more active during the pretreatment phase than rats treated with only vehicle; b) combined SCH 23390/eticlopride treatments produced a significant suppression of activity on all test days, and completely blocked the acute activating effects of cocaine; c) rats pretreated with cocaine displayed a greater activity response to the challenge injection of cocaine on day five than did rats pretreated with only vehicle (i.e., sensitization); d) concurrent pretreatment with the antagonist combination did not block the development of behavioral sensitization to cocaine; and e) pretreatment with the antagonist combination alone increased subsequent sensitivity to cocaine.

Consistent with previous research, repeated cocaine treatments resulted in the development of behavioral sensitization. Although the antagonist combination

completely blocked the acute locomotor-activating effects of cocaine, pretreatment with the antagonist combination did not block the development of behavioral sensitization to cocaine. These findings suggest that the repeated stimulation of dopamine receptors is not necessary for the development of cocaine-induced behavioral sensitization.

Accepted by: _____, Chairman

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A Thesis Presented to

the Faculty of the College of

Education and Behavioral Sciences

Morehead State University

In Partial Fulfillment

of the Requirement for the Degree

Master of Arts

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by

Todd Nichols Bonta

July 5, 1998

Accepted by the faculty of the College of Education and Behavioral Sciences, Morehead State University, in partial fulfillment of the requirements for the Master of Arts degree.

Director of Thesis

Master's Committee _____, Chairman

7-16-98
Date

ACKNOWLEDGEMENTS

I would like to thank Dr. Bruce Mattingly for his patience, guidance and assistance throughout this study. I would also like to thank Candace Himmler for her endless moral support and contributions to the many revisions and long hours spent working on this study.

Morehead State University TNB

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CHAPTER 1

INTRODUCTION

I. Psychostimulant Drugs and Behavioral Sensitization:

Drugs of abuse have become a increasing concern in our society. One category of drugs that receives a great deal of attention is that of psychostimulants. Today, stimulant drugs such as amphetamine and cocaine remain among the most widely abused of the many psychoactive compounds available (Robinson & Becker, 1986, Kalivas & Stewart, 1991; Stewart & Baldiani, 1993). When taken acutely, psychostimulants induce euphoria and heightened arousal, but after chronic use a variety of behavioral disorders may develop. Initially, psychostimulant abuse may result in craving, and a supersensitivity to other psychostimulants. With repeated self-administration, a pattern of compulsive drug-seeking and drug-taking behavior often occurs (Robinson & Berridge, 1993; Robinson & Becker, 1986; Berridge & Robinson, 1995). In addition, when repeatedly, or chronically administered, various behavioral disorders may result. Such disorders include panic attacks, delirium, and schizophrenic-like psychoses (Robinson & Becker, 1986, Robinson & Berridge,1993; Kalivas & Stewart, 1991). Although these disorders may subside if drug use is discontinued, they have been shown to resurface as many as ten years later if drug use is reinstated (Kalivas et al,1991; Ellinwood, 1967; Kramer, Fischman, & Littlefield, 1967). Thus, it is apparent that after chronic use of psychomotor stimulants,

long lasting alterations in the central nervous system occur (Mattingly, Gotsick & Salmanca, 1988).

Repeated psychomotor stimulant treatment in animals produces behavioral sensitization (Kalivas & Stewart, 1991; Robinson & Becker, 1986; Segal, 1975). Behavioral sensitization is said to occur when the same dose of a drug, repeatedly administered, produces a progressively greater behavioral effect. Once established, this behavioral supersensitivity is persistent for weeks or even months (Browne & Segal, 1977; Peris & Zahniser, 1987). For example, when rats are initially injected with cocaine, a modest increase in locomotor activity is usually elicited. After repeated treatments, however, the same dose of cocaine produces a significantly greater hyperactivity response (Angrist, 1983; Mattingly, Hart, Lim, & Perkins, 1994; Segal & Schuckit, 1983). In addition, recent evidence suggests that the rewarding effects of psychostimulant drugs may also become sensitized with repeated drug administrations (Lett 1989; Pierre & Vezina, 1997).

Neurobiological changes that mediate behavioral sensitization in rats are widely thought to be the same as those that produce the behavioral disorders associated with psychostimulant abuse in humans (Kalivas & Stewart, 1991; Robinson & Becker, 1986). In addition, these neurobiological changes may also be responsible for the intense craving and compulsive drug-seeking behavior that develops in humans after chronic psychostimulant abuse (Robinson & Berridge, 1993). Consequently, current

research is seeking to determine the neurobiological mechanisms which mediate the development and persistence of behavioral sensitization.

II. Dopamine Receptors and Dopamine Mediation of Behavioral Sensitization:

The rewarding and activating effects of psychostimulant drugs appear to be mediated by the dopaminergic neurotransmitter system (Wise & Bozarth, 1985; Wise & Bozarth, 1987). Psychostimulant drugs act to block the re-uptake and /or promote the release of dopamine into the synaptic cleft, and this action in forebrain dopamine terminal fields is thought to mediate much of the acute locomotor stimulant effect of these drugs (Kalivas & Stewart, 1991). The dopamine neurons of primary interest in the study of behavioral sensitization are located in the ventral tegmentum of the mesencephalon and were originally categorized as the A9 and A10 cell clusters. The A10 region is localized predominantly to the ventral tegmental area, and projects to the structures closely associated with the limbic system, most prominently the ventromedial portion of the striatal complex referred to as the nucleus accumbens, but also the olfactory tubercle, septal nucleus, and other limbic related areas (White, 1996). This system is considered separate from the nigrostriatal dopamine system in which the dopamine cell bodies in the A9 region are localized almost exclusively to the substantia nigra pars compacta, which projects to the neostriatum (Kalivas & Stewart, 1991).

The acute motor stimulant effects of psychostimulant drugs such as amphetamine and cocaine are believed to result from activation of the mesolimbic dopamine system which arises from A10 dopamine neurons to innervate the nucleus accumbens and other limbic brain structures (Steketee, Striplin, Murray, & Kalivas 1990). Despite the overlapping anatomy of the nigrostriatal and mesolimbic dopamine systems, each system appears to subserve distinct aspects of behavior. Current research has indicated that the nigrostriatal dopamine system facilitates motor preparatory processes and also stereotypic behaviors in rats. In contrast, the mesolimbic dopamine system facilitates the impact of stimulus-reward associations on behavior involved in incentive motivational processes, drug abuse, and craving (Robinson & Berridge, 1993; White 1996).

Recent advances in molecular biology have revealed multiple dopamine receptor subtypes (Civelli, Bunzow, & Grandy, 1993; Gingrich & Caron, 1993). Researchers have now distinguished five distinct subtypes of dopamine receptors. These five subtypes, however, can be divided into two families based upon molecular, biochemical, and pharmacological properties. The D1 and D5 receptor subtypes are alike in that they are found post-synaptically and stimulate adenlate cyclase enzyme activity. The D2 subfamily includes the D2, D3, and D4 receptor subtypes. The D2, D3, and D4 subtypes are similar in that they are located both pre- and post-synaptically and are either unlinked or inhibit the adenlate cyclase enzyme (Schwartz, Giros, Martres, & Sokoloff, 1992). Due to the similarities of these receptor subtypes,

D1 or D2 will refer to D1-type or D2-type receptors rather than specific D1 or D2 receptor subtypes. Currently, a number of drugs are available that are relatively selective to either the D1-type or the D2-type receptor families. However, few drugs are available that are sufficiently selective for individual receptors within either family.

Over the past decade, many researchers have focused their attention on discovering how different dopamine receptor types are involved in mediating the development of behavioral sensitization to psychostimulant drugs. Conceptualizing the role of various receptor sub-types may be important to the development of psychotherapeutic drugs with fewer side effects. In addition, an understanding of the involvement of these receptors in the development of behavioral sensitization may allow more effective methods of treating drug abuse to be developed.

III. Dopamine Antagonists and Behavioral Sensitization to Apomorphine and Amphetamine:

Most drugs that induce behavioral sensitization, either directly (e.g. apomorphine) or indirectly (e.g. cocaine, amphetamine) result in an increased stimulation of both dopamine D1 and D2 receptor subtypes. One approach to study the involvement of individual receptor subtypes in the development of sensitization has been to administer a drug that selectively blocks or antagonizes a particular receptor concurrently with a psychostimulant drug. Most of the research using this strategy suggests that repeated stimulation of D1 receptors is critical to the development of

sensitization. For example, the development of behavioral sensitization to amphetamine is prevented by the co-administration of the selective D1 antagonist, SCH-23390 (Stewart & Vezina, 1989). In contrast, co-administration of D2 dopamine receptor antagonists (e.g. sulpiride, pimozide, metoclopromide, or RO-22-2586) does not block behavioral sensitization to amphetamine (Drew & Glick, 1990; Stewart & Vezina, 1989; Vezina & Stewart, 1989). Similarly, the development of behavioral sensitization to the direct D1/D2 agonist apomorphine is also prevented by the co-administration of dopamine D1, but not D2 receptor antagonists (Mattingly, Rowlett, Graff & Hatton, 1991). Taken together, these findings suggest that D1 receptor stimulation mediates the development of sensitization.

IV. Dopamine Agonists and Behavioral Sensitization:

In addition to using selective dopamine antagonists, researchers have also used drugs that directly and selectively activate a particular subfamily of dopamine receptors to study receptor mechanisms mediating the development of behavioral sensitization. Based upon the dopamine antagonist studies discussed previously, it would be predicted that the repeated stimulation of dopamine D1-type, but not D2-type, receptors would result in the development of behavioral sensitization. The results of these selective agonist studies, however, indicate that receptor involvement in mediating the development of sensitization is more complex than initially conceived. For example, the acute administration of the selective dopamine D1-type receptor

agonist, SKF 38393, inhibits locomotor activity in rats, and this inhibition does not change with repeated daily treatments (Mattingly, Rowlett, & Lovell, 1993). On the surface, this finding appears inconsistent with the view that D1 receptor stimulation is responsible for sensitization. However, numerous studies have indicated that dopamine D1 and D2 receptors interact and that many dopamine-mediated behaviors are not expressed unless both receptor subtypes are stimulated (White, 1987). Consistent with this view, rats previously treated chronically with SKF 38393 display cross-sensitization to the activating effect of the direct-acting D1/D2 dopamine receptor agonist apomorphine (Mattingly et al., 1993). Thus, consistent with the antagonist findings, repeated stimulation of dopamine D1-type receptors does appear to induce a sensitized response. This sensitized response, however, is only expressed when both D1 and D2 receptors are activated (Mattingly et al., 1993).

As mentioned, based upon the antagonist findings, it would be predicted that repeated stimulation of dopamine D2-type receptors should not result in the development of behavioral sensitization. In contrast to this prediction, numerous studies have demonstrated that the repeated administration of the dopamine D2-type agonist, quinpirole induces sensitization (Mattingly et al., 1993; Szechtman, Talangbayan, & Eilam, 1993), and cross-sensitization to apomorphine (Mattingly et al., 1993). Moreover, the D2-type agonist bromocriptine also produces sensitization with repeated administration (Hoffman & Wise, 1992). These findings appear to be in direct conflict with the antagonist studies discussed previously indicating that D2

receptor stimulation is not necessary for the development of sensitization to either apomorphine or amphetamine (Drew & Glick, 1990; Stewart & Vezina, 1989; Vezina & Stewart, 1989). However, subsequent research indicated that the development of sensitization the D2-type agonists, quinpirole and bromocriptine, can be prevented with concurrent treatments with drugs that block D1-type receptors (Mattingly et al., 1993; Wise & Carlezon, 1994). These latter findings suggest that D2 receptor stimulation induces sensitization indirectly through D1 receptors. Together with the antagonist findings, the selective agonist results suggest that although dopamine D2 receptor stimulation may contribute to the development of behavioral sensitization, repeated dopamine D1 receptor stimulation is both necessary and sufficient for the induction of behavioral sensitization (Mattingly et al., 1993).

V. Dopamine Receptor Involvement in Cocaine-Induced Behavioral Sensitization:

It is generally accepted that nearly all drugs that directly or indirectly stimulate dopamine receptors induce behavioral sensitization with repeated stimulation (Kalivas & Stewart, 1991; Robinson & Becker, 1986; Robinson & Berridge, 1993). This has led many researchers to conclude that sensitization is a unitary process mediated by common mechanisms within the dopaminergic system. The research discussed previously with selective dopamine receptor agonists and antagonists along with work with amphetamine and apomorphine, collectively suggests that a critical factor in the development of sensitization to all drugs is the repeated stimulation of dopamine D1-

type receptors. For the most part, sensitization research with cocaine has been consistent with this view. For example, White and colleagues have demonstrated that repeated cocaine treatments result in a transient subsensitivity of dopamine D2 autoreceptors, and a long-lasting increase in the sensitivity of dopamine D1 receptors in the nucleus accumbens (Henry & White, 1991;White, 1996). These electrophysiological findings, of course, are consistent with the conclusions drawn from previous research with amphetamine and apomorphine (Drew & Glick, 1990; Vezina & Stewart, 1989; Stewart & Vezina, 1989). However, recent research which has attempted to block the development of cocaine-induced sensitization with selective dopamine antagonists has been inconsistent with these findings. For example, Mattingly and colleagues were unable to prevent the development of sensitization to cocaine with the selective dopamine D1-type receptor antagonist, SCH 23390 or the D2-type antagonist, sulpiride (Mattingly, Hart, Lim & Perkins, 1994; Mattingly, Rowlett, Ellison & Rase, 1996). Similar findings have also been reported using mice (Kuribara & Uchihashi, 1993). These antagonist findings suggest that, unlike other dopamine agonists such as amphetamine and apomorphine, stimulation of dopamine D1-type receptors is not critical to the development of sensitization to cocaine. Moreover, these discrepant results with cocaine suggest that the development of behavioral sensitization to dopamine agonists may not be mediated by common neurochemical mechanisms.

Although selective dopamine antagonists are ineffective in preventing the development of cocaine-induced behavioral sensitization, a recent study has found that high doses of the moderately selective dopamine D2-type antagonist, haloperidol, does prevent the development of cocaine-induced behavioral sensitization (Mattingly et al., 1996). This finding is perplexing because highly selective D2-type antagonists do not block the induction of sensitization to cocaine. However, since a very high dose of haloperidol was used, it is possible that at this dose both D1 and D2-type receptors were antagonized (Mattingly et al., 1996). If so, then this would suggest that cocaine-induced behavioral sensitization may develop through the repeated stimulation of either D1 or D2-type receptors. Thus, blocking sensitization to cocaine would require simultaneously blocking both receptor subtypes. It should be noted, however, that in addition to blocking dopamine receptors, haloperidol is also an antagonist at serotonin receptors and has a high affinity for sigma receptors (O'Dell et al., 1990; Quiron et al., 1992). Consequently, the exact mechanisms responsible for haloperidol's effectiveness in preventing cocaine-induced sensitization remain unclear.

VII. Purpose of Present Study:

As discussed above, the development of sensitization to cocaine appears to be mediated differently from other dopamine agonists. Unlike sensitization to amphetamine and apomorphine, which appears to be mediated exclusively by stimulation of dopamine D1 receptors, it appears that cocaine-induced sensitization

may develop through the repeated stimulation of either dopamine receptor subtype. The purpose of the present study, therefore, was to test this latter hypothesis by determining whether cocaine-induced behavioral sensitization could be prevented by selectively blocking both D1 and D2 receptors concurrently. Consequently, groups of rats were repeatedly given either cocaine or vehicle in combination with a cocktail of the D1 antagonist, SCH 23390 and the D2 antagonist, eticlopride or vehicle. Following this chronic pretreatment phase, all rats were given a challenge injection of cocaine alone to test for sensitization. If the development of cocaine-induced behavioral sensitization is mediated by dopamine receptors, then the combination of SCH 23390 and eticlopride should prevent the development of sensitization.

CHAPTER 2

METHODS

Subjects

Forty-eight male Wistar albino rats were obtained from Harlan Sprague-Dawley, Inc. Indianapolis, Indiana. The rats weighed between 250-300g prior to testing. The rats were housed individually in standard wire-mesh cages in a temperature-controlled colony room with a 12 hr light-dark cycle. All testing was conducted during the light phase of the cycle. The rats were housed in the colony room for at least one week prior to the beginning of the experiment. During this time, each rat was weighed and handled for five min every other day. All rats had food and water available ad libidum.

Apparatus

Activity measures were taken in four square Med-Associates open field test chambers (Med-Associates model OFA-163, see Figure 1). These chambers were approximately 41 x 41 cm., and equipped with a 16 x 16 array of infrared photocell beams positioned 2.5 cm. above the floor and a single array of 16 photocells mounted 10 cm. above the floor. A clear cylindrical acrylic chamber was positioned inside the outer square chamber. Output from each individual photocell array was connected to a Gateway 2000 (P5-75) microcomputer through a Med-Associates interface, located in an adjacent room. Using Med-Associates software, the following measures were

recorded during each test session: distance traveled, stereotypical counts, and vertical counts (rearings).

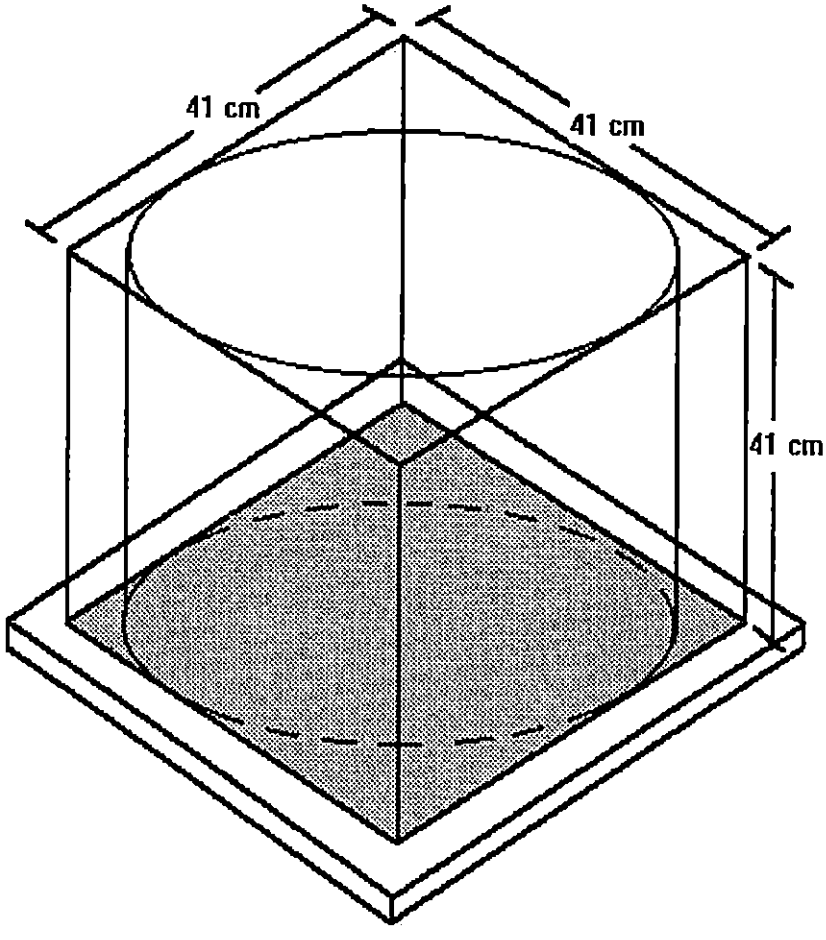

Figure 1. Med-Associates locomotor activity testing chambers.

Drugs

The following drugs were dissolved daily in distilled H_2O: cocaine hydrochloride, eticlopride and SCH 23390. All drugs were injected subcutaneous (S.C.) or intraperitoneal (I.P.) in a volume of 1 ml/kg. All drug dosages were calculated based upon salt weight of the drug. Control injections were given using the same vehicle, route of administration, and volume as the corresponding drug injection.

Design & Procedure

The design of the experiment was a 2 x 2 factorial design, combining two antagonist doses and two cocaine doses. There were 12 rats per group and all rats were randomly assigned and counterbalanced within the 4 pretreatment groups. A summary of the experimental design is shown below in Table 1 and the counterbalancing procedure is depicted in Table 8, Appendix B.

Table 1

Experimental Design

Pretreatment groups (2 X 2 Factorial Design)

	Second injection (I.P.)	
	COCAINE	VEHICLE
First injection (S.C.)		
SCH-23390/ ETICLOPRIDE	SE-C (N=12)	SE-V (N=12)
VEHICLE	V-C (N=12)	V-V (N=12)

The experiment was divided into two phases: a pretreatment phase, and a cocaine challenge test. During the pretreatment phase each rat was first injected S.C. with the selective D1 dopamine antagonist SCH-23390 (0.10 mg/kg) and the selective dopamine D2 antagonist eticlopride (0.10 mg/kg) in combination or vehicle. Twenty-five min later each rat was injected I.P. with cocaine (15 mg/kg), or an equivalent volume of vehicle. Five min after the cocaine injection, the rats were placed in the activity chambers for 60 min and tested for locomotor activity. This pre-treatment phase was repeated for four days.

Twenty-four hours after the pre-treatment phase, all rats were first given a vehicle injection, S.C., and 25 min later, subsequently administered a challenge injection of cocaine (10 mg/kg I.P.) to test for behavioral sensitization.

Data Analysis

Statistical tests included mixed-factor analyses of variance with drug treatment conditions as between-groups factors and activity test sessions and blocks within sessions as repeated measures. These analyses were supplemented, when appropriate, with Newman-Keuls post hoc tests.

CHAPTER 3

RESULTS

Pretreatment Sessions- Days 1-4

Distance Traveled:

The mean distance traveled in cm for each of the four pretreatment groups for the four 60 min pretreatment sessions is depicted in Figure 2, and the within session activity of the four pretreatment groups on Day 1 through Day 4 is depicted in Figure 3. A mixed factor analysis of variance was performed on the mean distance traveled data with drug treatment conditions as between-groups factors and activity test sessions and blocks within sessions as repeated measures (see Appendix A, Table 2).

As may be seen in Figure 2, rats treated with the antagonist combination (i.e., Sch/Etic-Vehicle, Sch/Etic-Cocaine groups) were significantly less active than the vehicle control rats, [antagonist effect: $F(1, 44) = 200.35$, $p < .0001$]. Although rats treated with only cocaine (i.e., Vehicle-Cocaine) were significantly more active than the vehicle control rats (i.e., Vehicle-Vehicle), cocaine did not significantly increase the activity of rats concurrently treated with the antagonist combination [cocaine effect: $F(1, 44) = 83.43$, $p < .0001$; Antagonist x Cocaine interaction: $F(1, 44) = 82.22$, $p < .0001$]. That is, the antagonist pretreatment completely blocked the acute activating effect of cocaine on each day. As shown in Figure 3, the activity of the Vehicle-Cocaine and the Vehicle-Vehicle groups decreased across the four 15 min blocks within each 60 min session, whereas the activity of the two antagonist groups

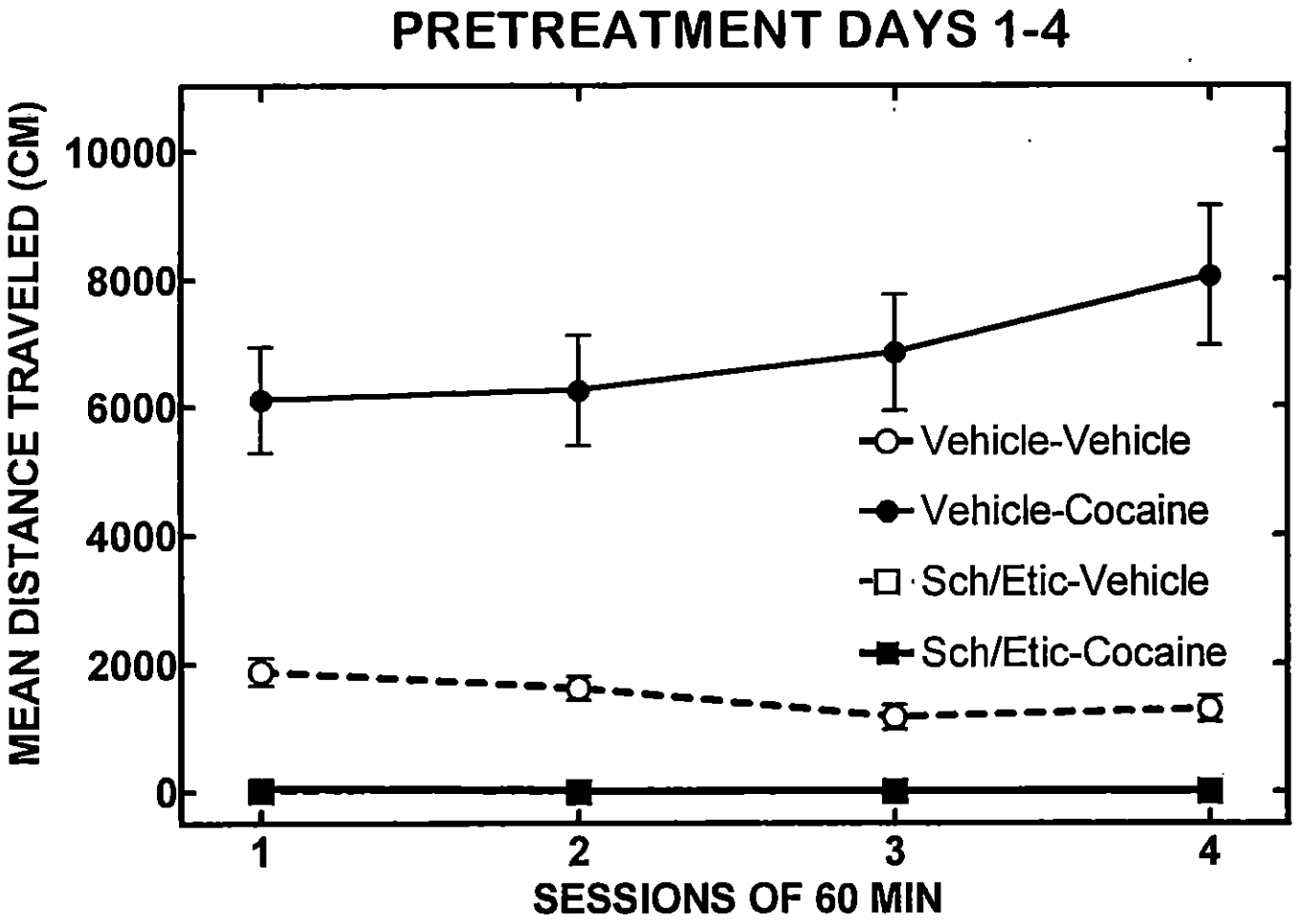

Figure 2. Mean distance traveled in centimeters (cm ± SEM) for each of the four pretreatment groups over the four 60 min pretreatment sessions. (the Sch/Etic-Vehicle and Sch/Etic-Cocaine groups overlap)

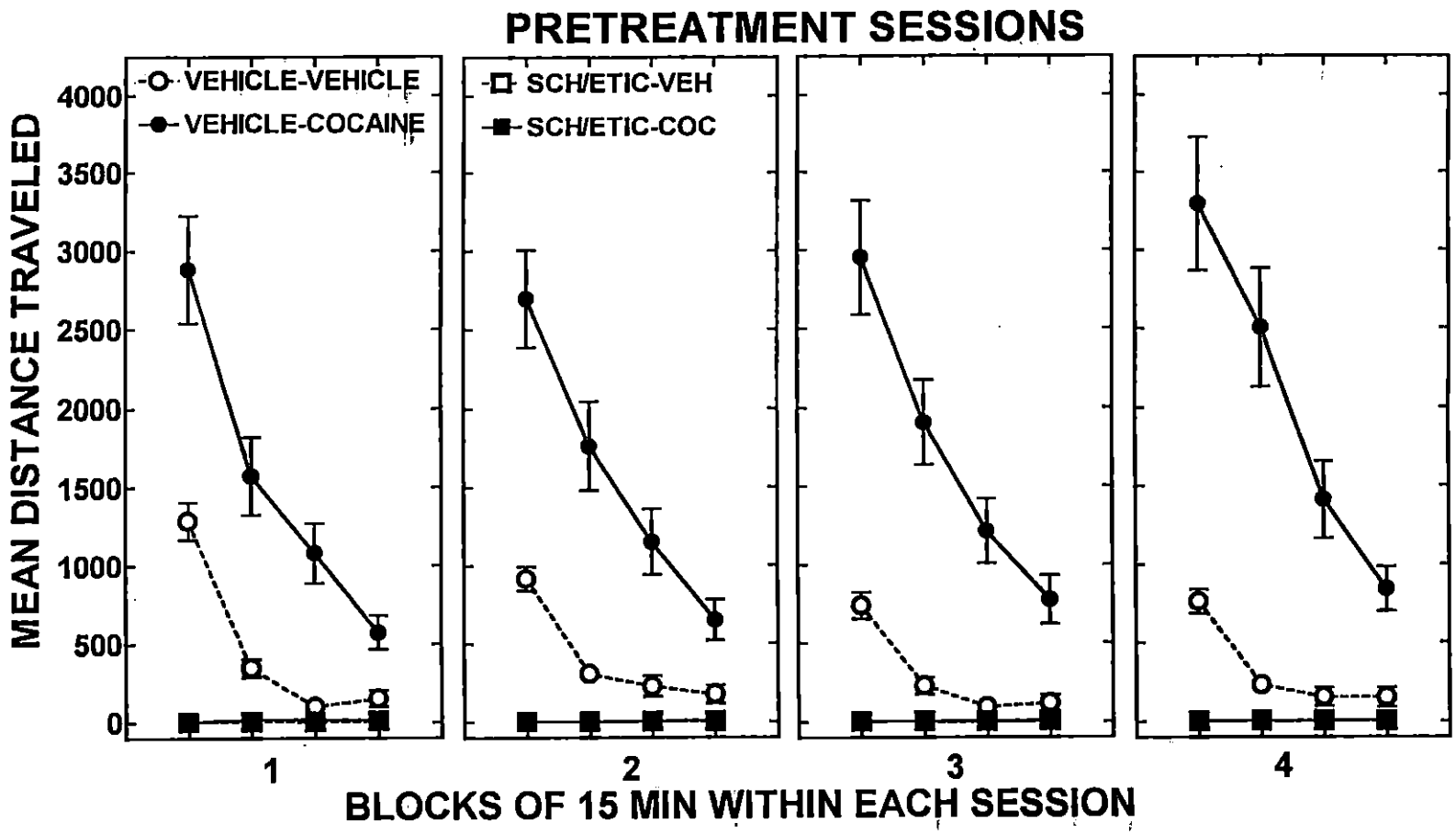

Figure 3. Mean distance traveled in centimeters (cm ± SEM) for each of the four pretreatment groups across the four 15 min blocks within each of the 60 min pretreatment sessions. (the SCH/ETIC-VEH and SCH/ETIC-COC groups overlap)

remained consistently low across blocks, [block effect: $F(3, 132) = 219.12$, $p < .0001$; Antagonist x Block interaction: $F(3, 132) = 221.12$, $p < .0001$; Cocaine x Block interaction: $F(3, 132) = 52.14$, $p < .0001$; Antagonist x Cocaine x Block interaction: $F(3, 132) = 52.73$, $p < .0001$]. Although the activity of rats treated with only cocaine tended to increase across days, this increase was not significant, [Cocaine x Day interaction: $F(3, 132) = 1.67$, $p > .05$]. Likewise, the activity of the other groups did not significantly change across days, as neither the day effect nor any of the interactions including day as a factor were significant (see Appendix A, Table 2).

Stereotypic Counts:

The mean number of stereotypic counts for each of the four pretreatment groups for the four 60 min pretreatment sessions is depicted in Figure 4, and the within session activity of the four pretreatment groups on Day 1 through Day 4 is depicted in Figure 5. A mixed factor analysis of variance was performed on the stereotypic data with drug treatment conditions as between-groups factors and activity test sessions and blocks within sessions as repeated measures (see Appendix A, Table 3).

As may be seen in Figure 4, the results for the stereotypic count data are similar to those obtained for the distance traveled data. That is, rats treated with the antagonist combination (i.e., Sch/Etic-Vehicle, Sch/Etic-Cocaine groups) were significantly less active than the vehicle control rats, [antagonist effect: $F(1, 44) = 489.21$, $p < .001$]. Although rats treated with only cocaine (i.e., Vehicle-Cocaine)

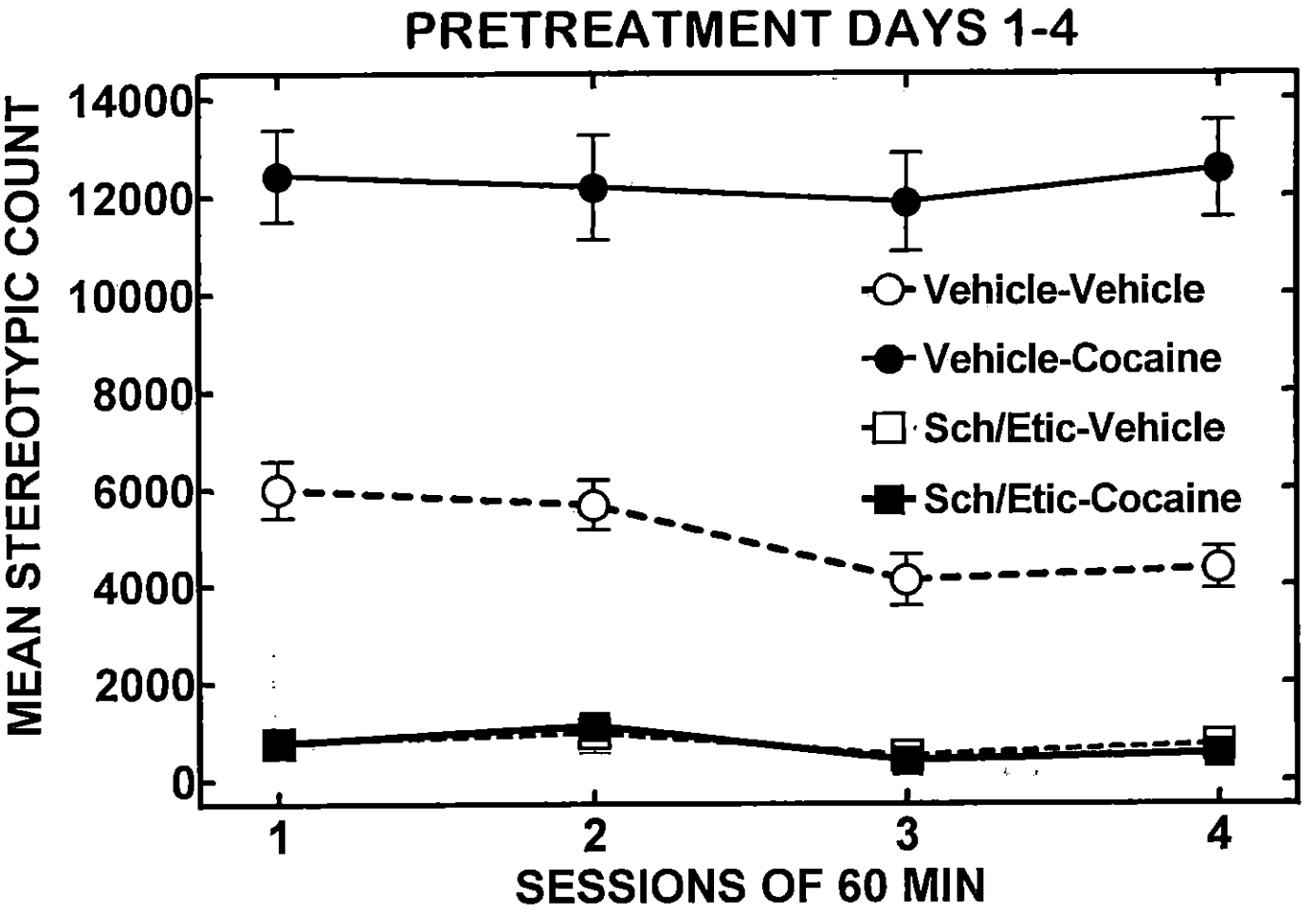

Figure 4. Mean stereotypic count (± SEM) for each of the four pretreatment groups over the four 60 min pretreatment sessions.

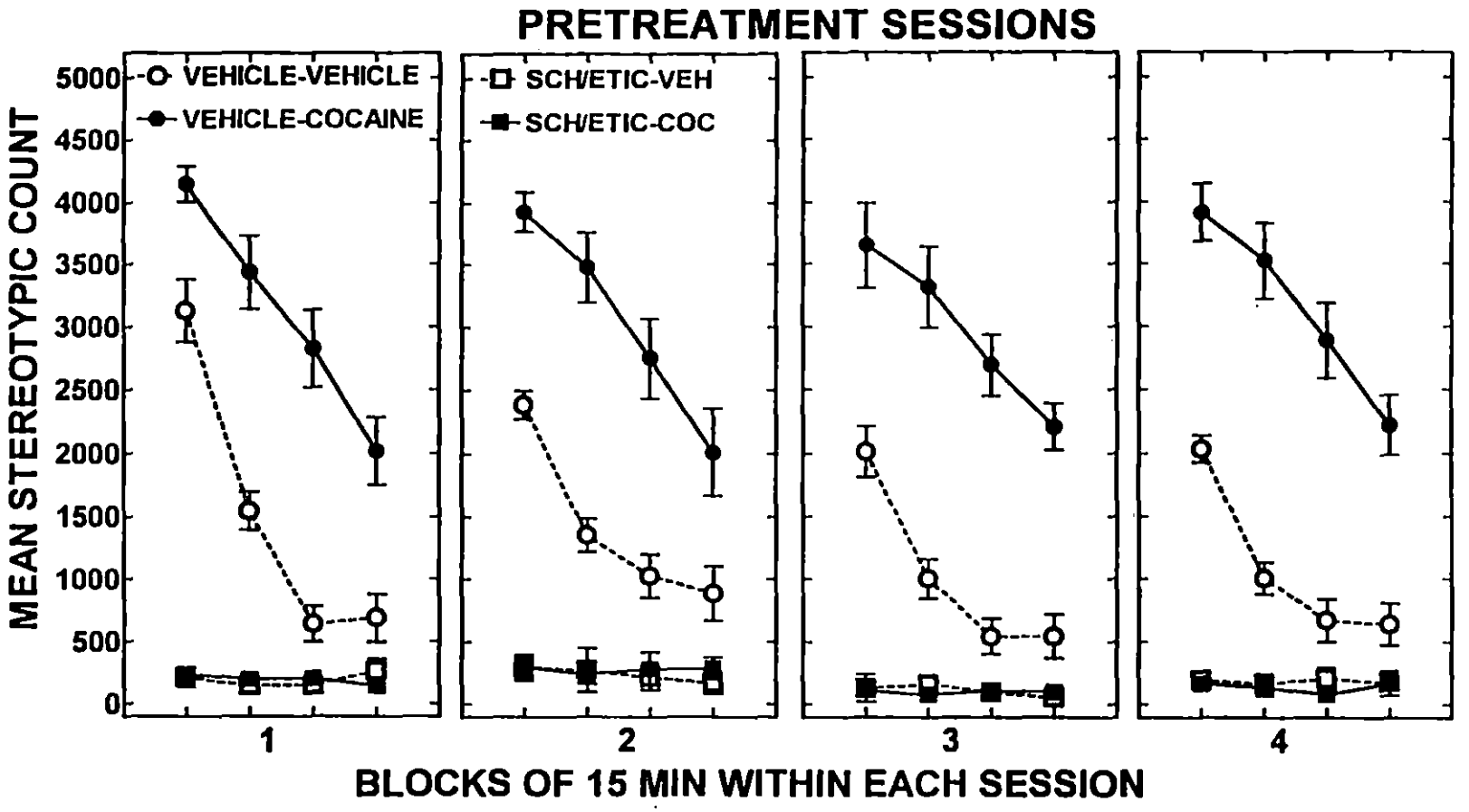

Figure 5. Mean stereotypic count (± SEM) for each of the four pretreatment groups across the four 15 min blocks within each of the four 60 min pretreatment sessions.

were significantly more active than the vehicle control rats (i.e., Vehicle-Vehicle), cocaine did not significantly increase the activity of rats concurrently treated with the antagonist combination [cocaine effect: $\underline{F}(1, 44) = 100.89$, $\underline{p} < .001$; Antagonist x Cocaine interaction: $\underline{F}(1, 44) = 102.60$, $\underline{p} < .0001$]. That is, the antagonist pretreatment completely blocked the acute activating effect of cocaine on each day. As may be seen in Figure 5, the activity of the Vehicle-Cocaine and Vehicle-Vehicle groups decreased across the four 15 min blocks within each 60 min session, whereas the activity of the Sch/Etic-Vehicle and Sch/Etic-Cocaine groups remained consistently low across blocks [block effect: $\underline{F}(3, 132) = 168.19$, $\underline{p} < .0001$; Antagonist x Block interaction: $\underline{F}(3, 132) = 152.57$, $\underline{p} < .0001$; Cocaine x Block interaction: $\underline{F}(3, 132) = 10.32$, $\underline{p} < .0001$; Antagonist x Cocaine x Block interaction: $\underline{F}(3, 132) = 10.82$, $\underline{p} < .0001$]. Although the activity of rats treated with only cocaine tended to increase across days, this increase was not significant, [Cocaine x Day interaction: $\underline{F} < 1.00$].

Rears:

Similar mixed factor Anovas were performed on the vertical activity or rearing data (see Appendix A, Table 4). The mean number of rears for the four pretreatment groups over the four 60 min sessions is depicted in Figure 6.

Again, the results for the rearing data are similar to the distance traveled and stereotypic data. As may be seen in Figure 6, That is, rats treated with the antagonist combination (i.e., Sch/Etic-Vehicle, Sch/Etic-Cocaine groups) were significantly less

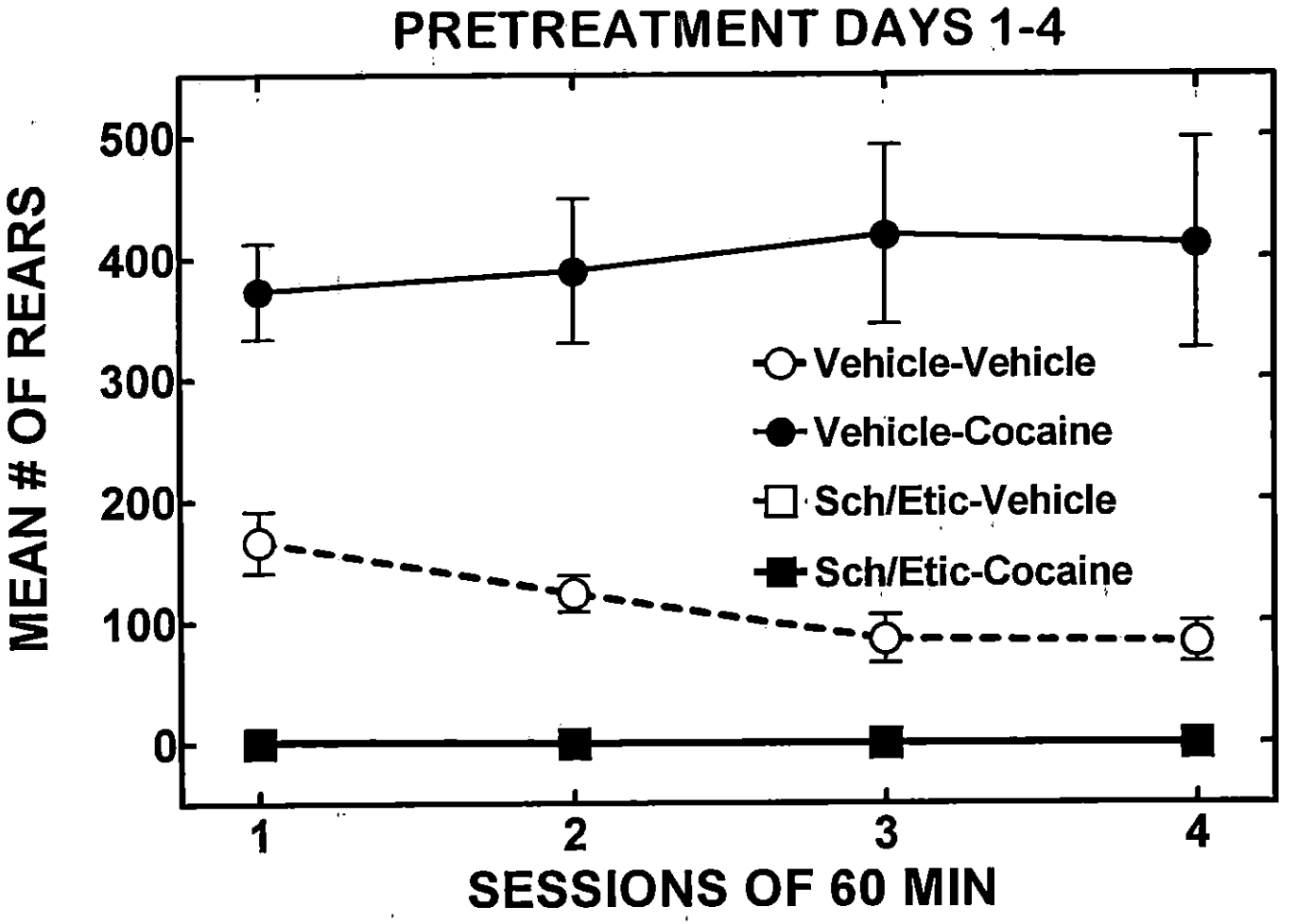

Figure 6. Mean number of rears (± SEM) for each of the four pretreatment groups over the four 60 min pretreatment sessions. (the Sch/Etic-Vehicle and Sch/Etic-Cocaine groups overlap)

active than the vehicle control rats, [antagonist effect: $F(1, 44) = 93.81$, $p < .001$]. Although rats treated with only cocaine (i.e., Vehicle-Cocaine) were significantly more active than the vehicle control rats (i.e., Vehicle-Vehicle), cocaine did not significantly increase the activity of rats concurrently treated with the antagonist combination [cocaine effect: $F(1, 44) = 28.93$, $p < .001$; Antagonist x Cocaine interaction: $F(1, 44) = 28.62$, $p < .0001$]. That is, the antagonist pretreatment completely blocked the acute activating effect of cocaine on each day. Figure 7 displays the rearing behavior of the four pretreatment groups across blocks of 15 min during the four pretreatment sessions. As shown in Figure 7, the activity of the Vehicle-Cocaine and Vehicle-Vehicle groups decreased across the four 15 min blocks within each 60 min session, whereas the activity of the Sch/Etic-Vehicle and Sch/Etic-Cocaine groups remained consistently low across blocks [block effect: $F(3, 132) = 138.03$, $p < .0001$; Antagonist x Block interaction: $F(3, 132) = 138.69$, $p < .0001$; Cocaine x Block interaction: $F(3, 132) = 14.40$, $p < .0001$; Antagonist x Cocaine x Block interaction: $F(3, 132) = 14.61$, $p < .0001$]. Although the activity of rats treated with only cocaine tended to increase across days, this increase was not significant, [Cocaine x Day interaction: $F(3, 132) = 1.21$, $p > .05$]. Likewise, the activity of the other groups did not significantly change across days, as neither the day effect nor of the interactions including day as a factor were significant (see Appendix A, Table 4).

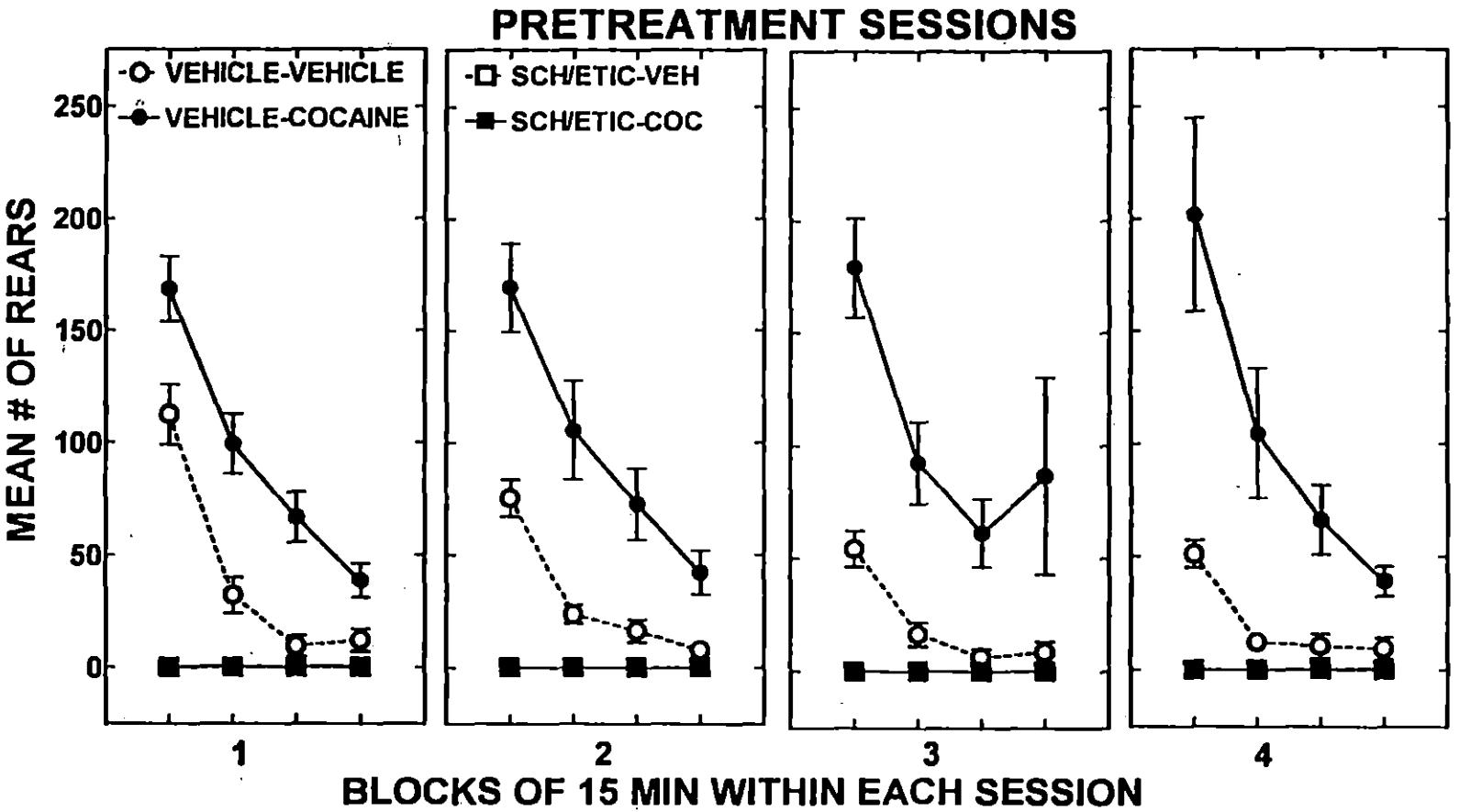

Figure 7. Mean number of rears (± SEM) for each of the four pretreatment groups across the four 15 min blocks within each of the 60 min pretreatment sessions. (the SCH/ETIC-VEH and SCH/ETIC-COC groups overlap)

Cocaine Challenge- Day 5

Distance Traveled:

A mixed factor analysis of variance was performed on the mean distance traveled data with drug treatment conditions as between-groups factors and blocks within sessions as a repeated measure (see Appendix A, Table 5). The mean distance traveled for the four pretreatment groups on the 60 min cocaine challenge test is depicted in Figure 8 and the within session activity of the groups is presented in Figure 9. As may be seen in Figure 8, overall, rats pre-exposed to cocaine for four days were significantly more active after the cocaine challenge injection than rats receiving cocaine for the first time [cocaine effect: $F(1, 44) = 12.15$, $p = .001$], particularly on the first three 15 min time blocks [cf. Figure 9; block effect: $F(3, 132) = 199.30$, $p < .0001$; Cocaine x Block interaction: $F(3, 132) = 8.85$, $p < .0001$]. More important, this cocaine pretreatment effect was not affected by concurrent antagonist treatments [Antagonist x Cocaine interaction: $F < 1.00$; Antagonist x Cocaine x Block interaction: $F < 1.00$]. In fact, rats treated with the antagonist combination were significantly more active on the cocaine challenge test than rats pretreated with only vehicle [antagonist effect: $F(1, 44) = 14.66$, $p < .001$]. Thus, rather than blocking the development of behavioral sensitization to cocaine, concurrent treatment with the antagonist combination appeared to increase subsequent behavioral sensitivity to cocaine.

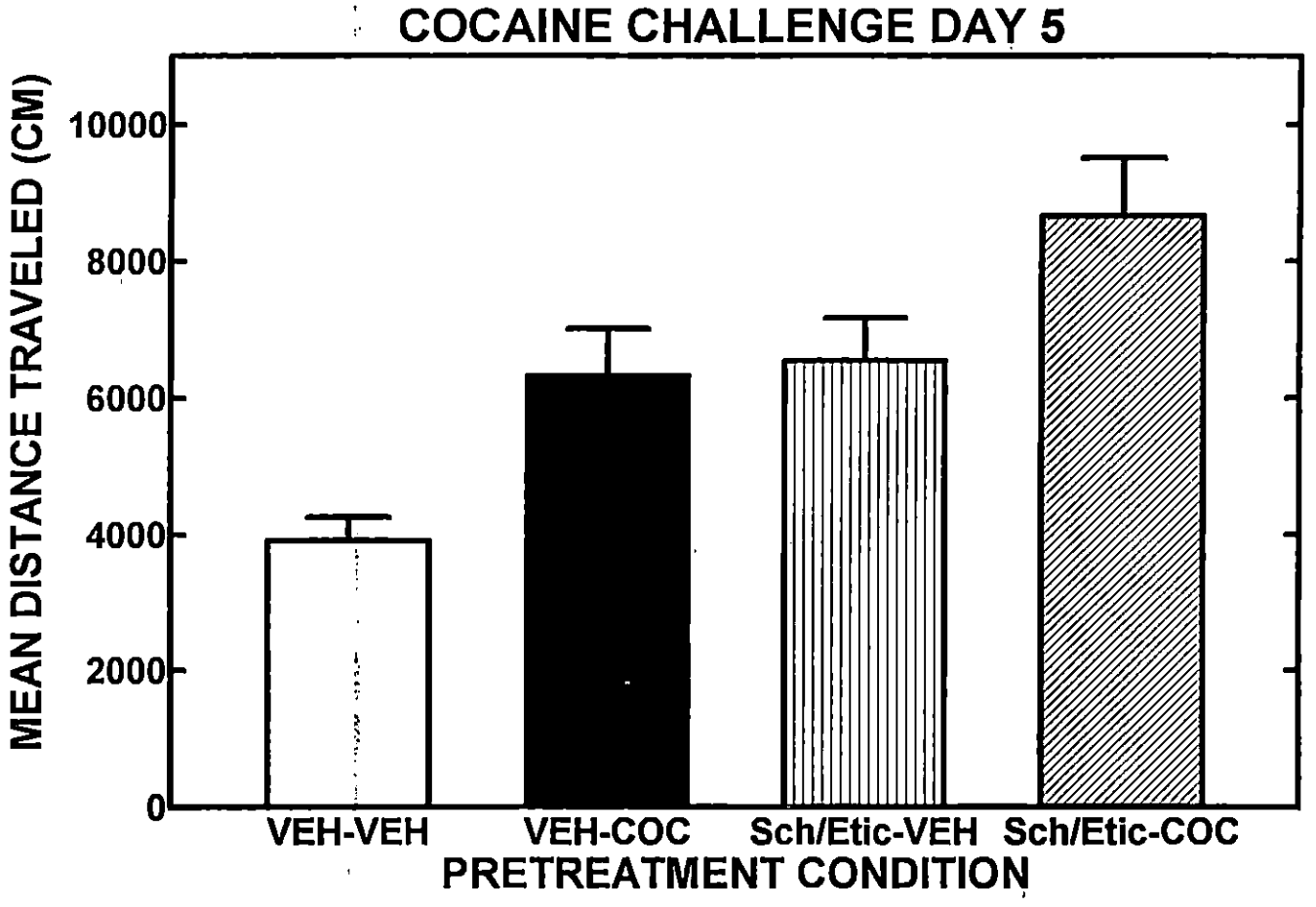

Figure 8. Mean distance traveled in centimeters (cm ± SEM) after a challenge injection of cocaine (10 mg/kg) for each of the four pretreatment groups over the 60 min session.

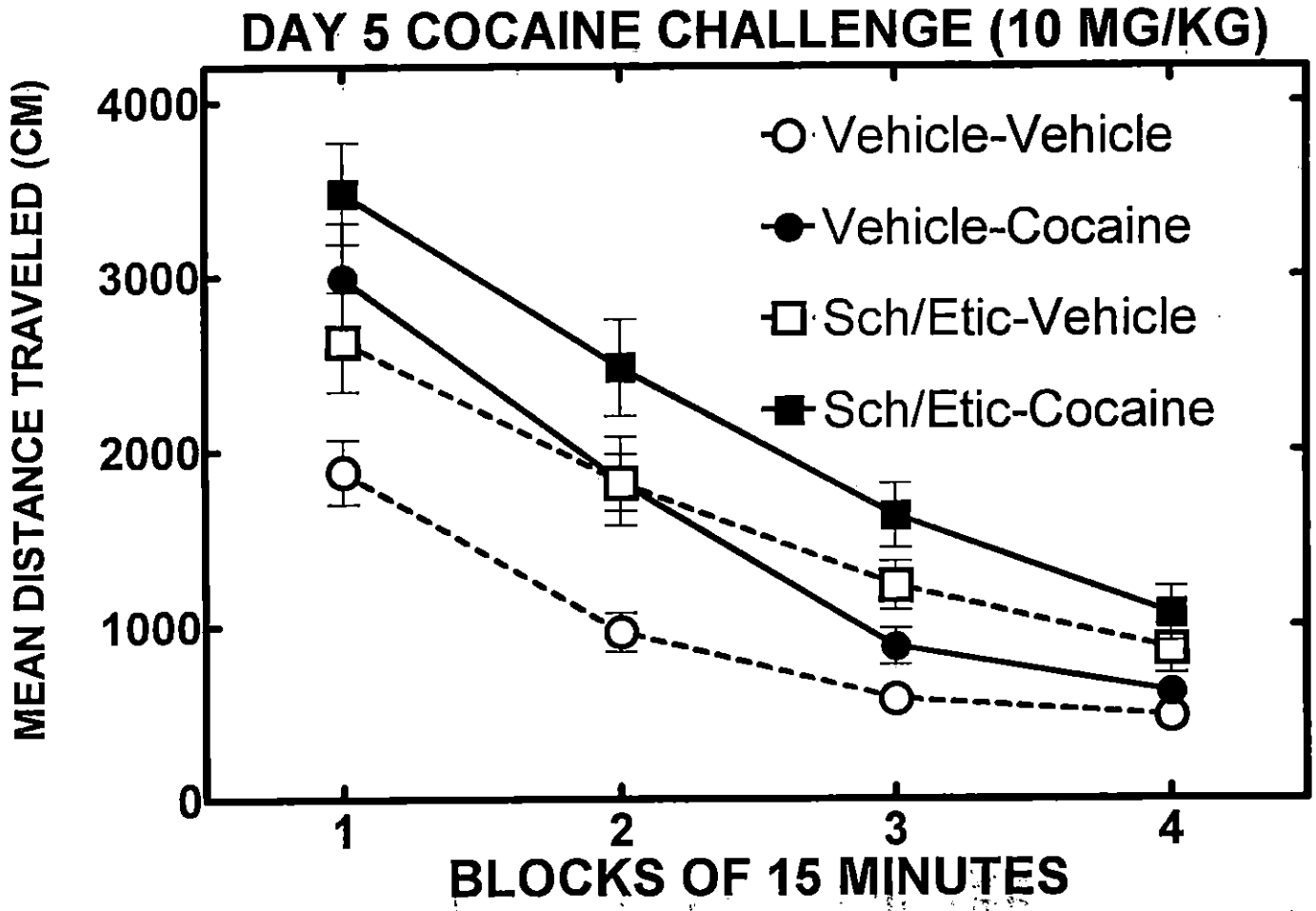

Figure 9. Mean distance traveled in centimeters (cm ± SEM) after a challenge injection of cocaine (10 mg/kg) for each of the four pretreatment groups across the four 15 min blocks within the 60 min session.

Stereotypic Counts:

The mean stereotypic counts for the four pretreatment groups during the 60 min cocaine challenge test are shown in Figure 10 and the within session stereotypic activity of the four pretreatment groups is displayed in Figure 11. As may be seen in Figure 10, overall, rats pretreated for four days with the antagonist combination were significantly more responsive to the cocaine challenge injection than rats that pre-exposed to cocaine or vehicle only [antagonist effect: $\underline{F}(1, 44) = 16.69$, $\underline{p} < .0001$]. As shown in Figure 11, however, this effect was greater on blocks 3 and 4 than on blocks 1 and 2, as the vehicle pretreated groups (Vehicle-Vehicle, Vehicle-Cocaine) stereotypy scores decreased across blocks at a greater rate than did the antagonist pretreated groups (Sch/Etic-Vehicle, Sch/Etic-Cocaine) [block effect: $\underline{F}(3, 132) = 114.09$, $\underline{p} < .0001$; Antagonist x Block interaction: $\underline{F}(3, 132) = 9.89$, $\underline{p} < .0001$]. More important, as may be seen in Figures 10 and 11, rats treated with cocaine did not display an increase in cocaine-induced stereotypy [cocaine effect: $\underline{F} < 1.00$; Cocaine x Block interaction: $\underline{F} < 1.00$] (see Appendix A, Table 6). That is, behavioral sensitization to cocaine did not develop using the stereotypic activity as a measure.

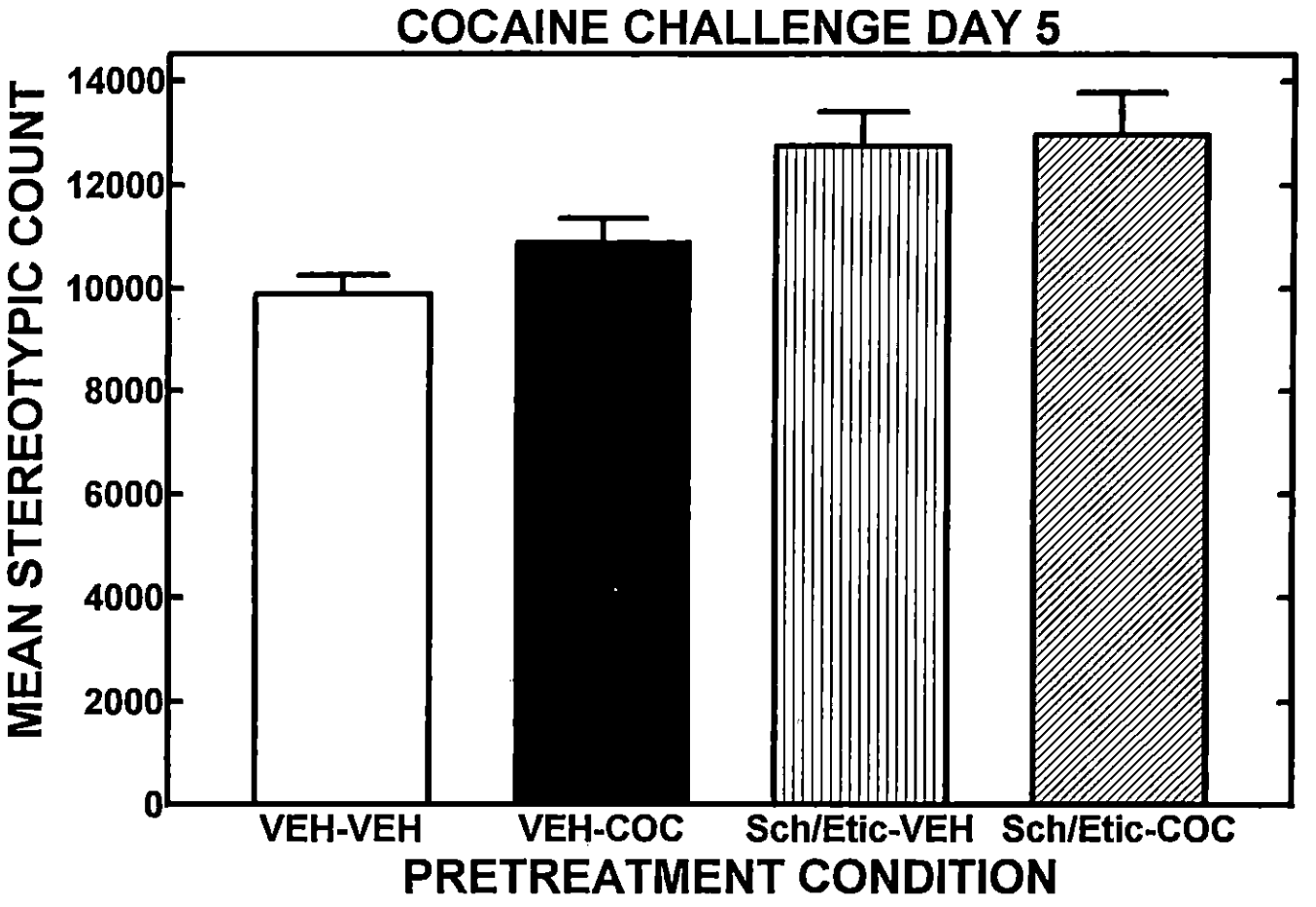

Figure 10. Mean stereotypic count (± SEM) after a challenge injection of cocaine (10 mg/kg) for each of the four pretreatment groups over the 60 min session.

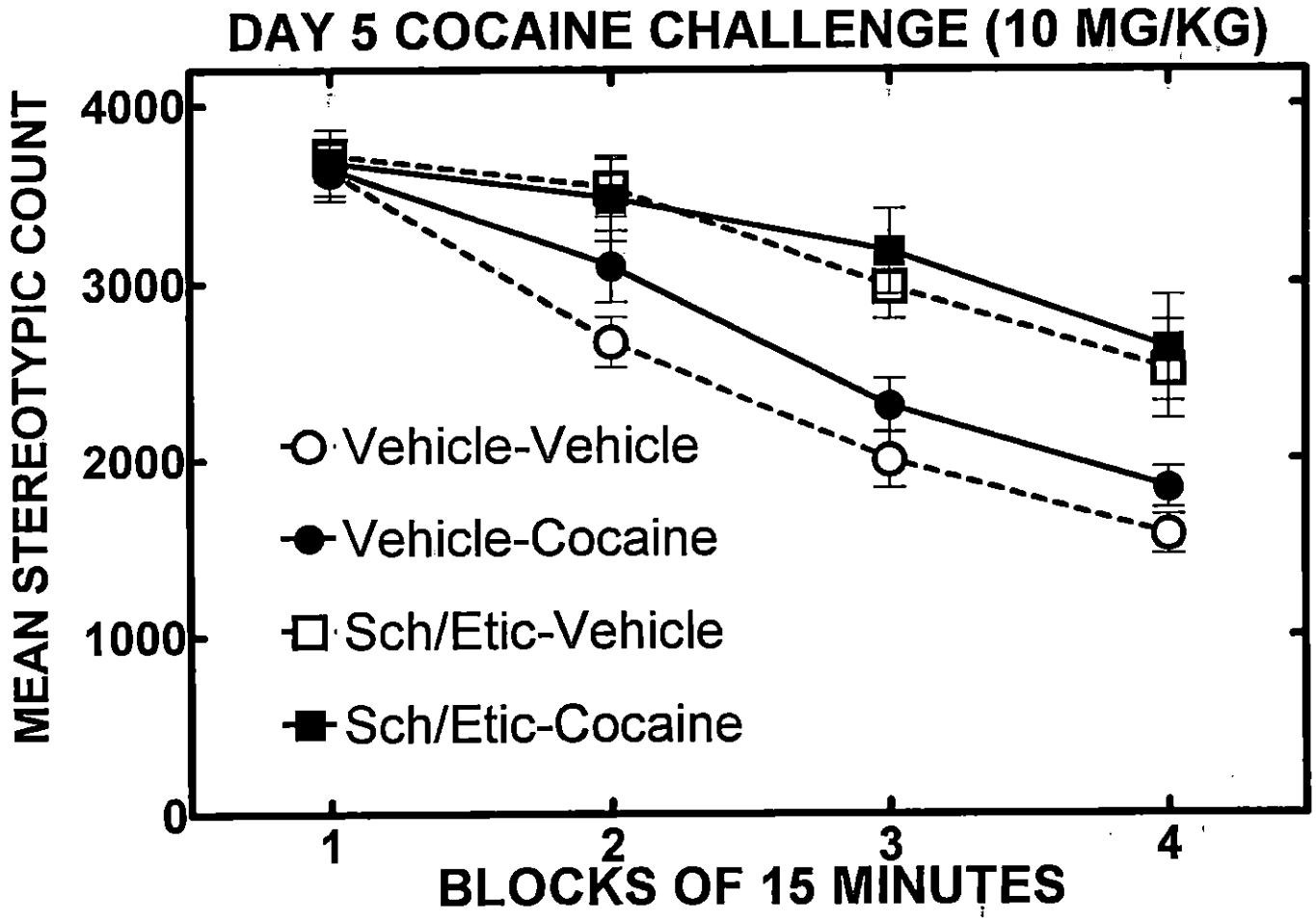

Figure 11. Mean stereotypic count (± SEM)after a challenge injection of cocaine (10 mg/kg) for each of the four pretreatment groups across the four 15 min blocks within the 60 min session.

Rears:

The mean number of rears for the four pretreatment groups following a challenge injection of cocaine are shown in Figure 12, and the within session rearing activity of the pretreatment groups is depicted in Figure 13. As may be seen, the antagonist pretreatment groups were significantly more responsive to the cocaine challenge on day five than vehicle or cocaine pretreatment groups [antagonist effect: $F(1, 44) = 16.86$, $p < .001$], particularly on the first three 15 min time blocks [cf. Figure 13; block effect: $F(3, 132) = 102.24$, $p < .0001$; Antagonist x Block interaction: $F(3, 132) = 4.51$, $p < .01$] Although cocaine pretreatment did not result in an overall increase in rearing activity [cocaine effect: $F(1,44) = 2.63$, $p > .05$], rats pre-exposed to cocaine did display significantly greater rearing activity on the first 15 min time block compared to the vehicle pretreated rats [Cocaine x Block interaction: $F(3,132) = 7.70$, $p < .0001$]. Thus, similar to the results using distance traveled as a behavioral measure, these data suggest that pretreatment with cocaine produced sensitization to cocaine-induced rearing behavior, and this effect was not blocked by concurrent treatment with the antagonist combination.

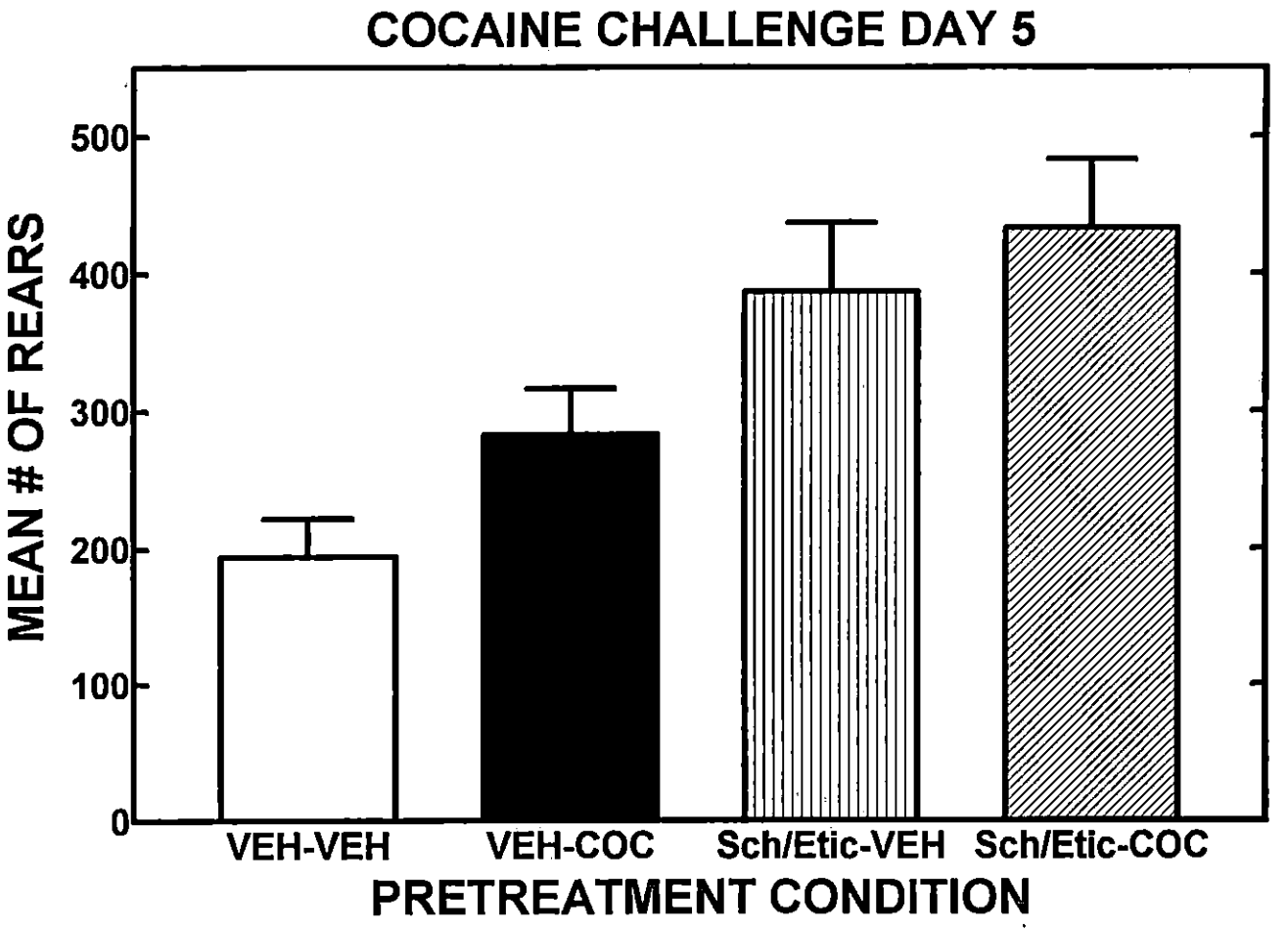

Figure 12. Mean number of rears (±SEM) after a challenge injection of cocaine (10 mg/kg) for each of the four pretreatment groups over the 60 min session.

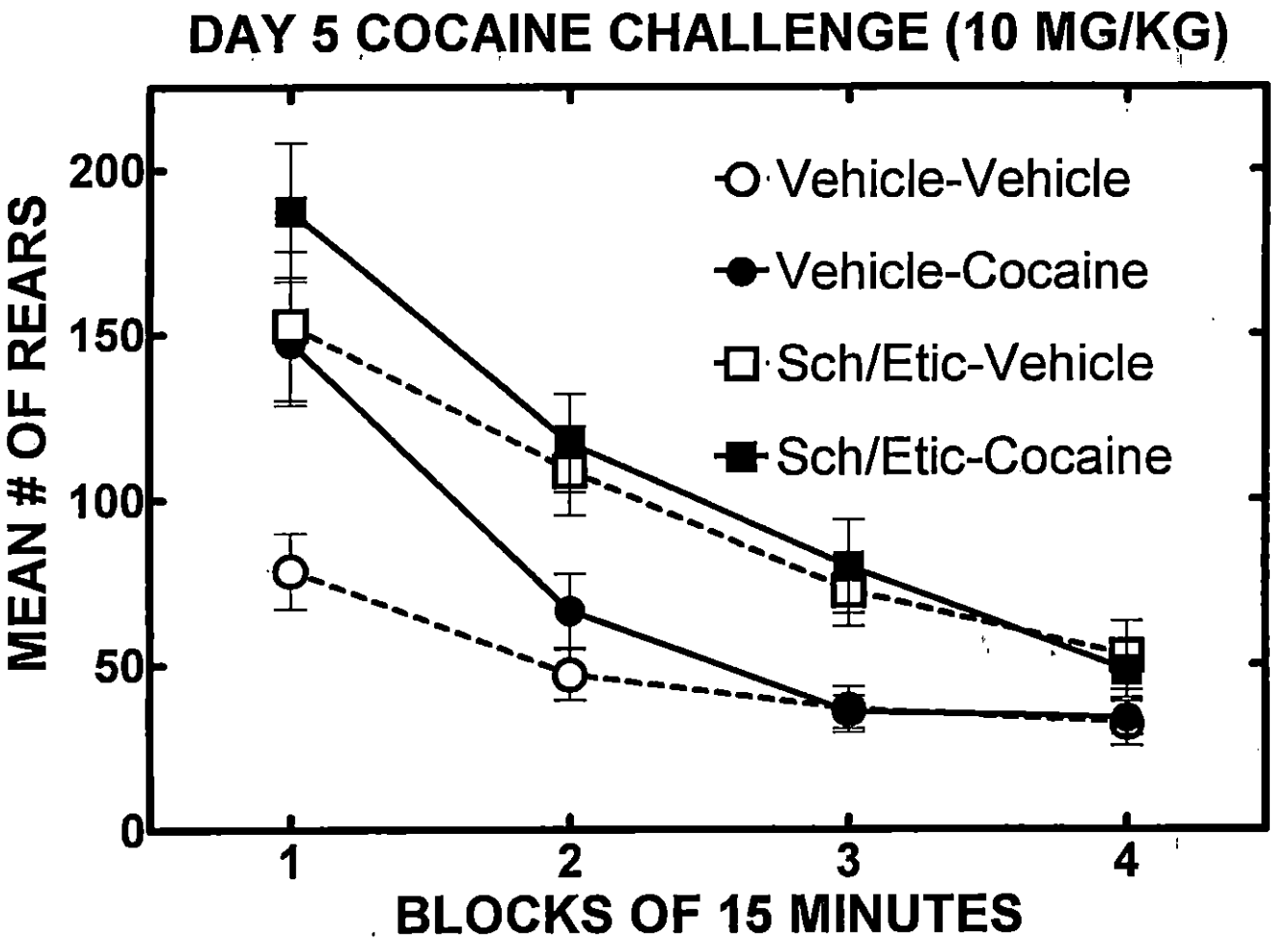

Figure 13. Mean number of rears (±SEM) after a challenge injection of cocaine (10 mg/kg) for each of the four pretreatment groups across the four 15 min blocks within the 60 min session.

CHAPTER 4

DISCUSSION

I. Behavioral Sensitization to Cocaine:

Behavioral sensitization is defined as a progressive increase in behavioral sensitivity to a drug as a result of repeated administration. Depending upon design, two different methods have been used to measure the development of behavioral sensitization. One method has been to demonstrate a progressively greater behavioral effect of a drug with each succeeding administration. For example, numerous studies have demonstrated that the locomotor-activating effects of the direct dopamine agonist, apomorphine increase with each succeeding administration (Damianopoulos & Carey, 1993; Mattingly et al., 1988; Rowlett, Mattingly, & Bardo, 1991). An alternative method of measuring behavioral sensitization has been to compare the effects of a challenge injection of the drug in rats previously treated with the drug to those receiving the drug for the first time. If sensitization develops, then animals pre-exposed to the drug should display a significantly greater behavioral response to the drug than animals receiving the drug for the first time. Numerous studies using apomorphine, cocaine, and amphetamine have demonstrated the development of behavioral sensitization in this way (Kalivas & Stewart, 1991; Martin-Iverson & Reimer, 1994; Robinson & Becker, 1986; Segal, 1975).

In the present study, both methods of measuring behavioral sensitization were used with three different measures of motor behavior. Consistent with previous

studies, rats previously treated with cocaine for four consecutive days displayed a significantly greater behavioral reaction to the cocaine challenge injection on Day 5 than rats receiving cocaine for the first time (Mattingly et al., 1996; White, Joshi, Koeltzow & Hu, 1998). In contrast, rats pretreated with cocaine did not display a progressive between-session increase in activity across the four pretreatment days. This discrepancy between the two measures of sensitization has been noted before (e.g., Martin-Iverson & Reimer, 1994). In the case of cocaine, sensitization has been most frequently observed after a challenge test, whereas between session increases in cocaine-induced activity are often not observed (Hooks, Jones, Smith, Neill & Justice, 1991; Mattingly et al., 1994). One factor that may contribute to this discrepancy is the dose of cocaine used. For example, on the challenge test, a 10 mg/kg dose of cocaine was used, whereas in the pretreatment phase, a 15 mg/kg dose was used. It is possible that the higher dose of cocaine produced a ceiling effect with respect to activity. That is, at this dose, the acute activating effects of cocaine may have been too high to observe further increases in activity. By using a lower dose on the challenge test, differences in sensitivity may have been easier to observe. In fact, this was the rationale for using a lower dose for the challenge test. Although a lower dose could have been used during pretreatment to avoid a possible ceiling effect, the 15 mg/kg dose of cocaine has been shown to be the most effective dose for inducing maximum sensitization (Kalivas, Duffy, DuMars & Skinner, 1988).

It should be noted that behavioral sensitization to cocaine was observed on the challenge test for the distance traveled and rearing measures, but not for the stereotypy measure. Although a few studies have reported sensitization to cocaine using stereotypy (Henry & White, 1995; McCreary & Marsden, 1993), the vast majority of cocaine-sensitization studies have used horizontal locomotion and rearing as behavioral measures (Fontanna, Post, Weiss & Pert, 1993; Kalivas et al., 1988; Mattingly et al., 1994; Mattingly et al., 1996). Consistent with these findings, behavioral sensitization to apomorphine is also observed using horizontal locomotion, but not using stereotypy as a behavioral measure (Mattingly, Gotsick & Marin, 1988). A great deal of evidence suggests that stereotypic responses induced by dopaminergic agonists is mediated by increased stimulation of dopamine receptors in the nigrostriatal dopamine pathway, whereas the locomotor-activating effects of dopamine agonists are mediated by increased stimulation of the mesolimbic pathway (White, 1996). If so, then the current findings suggest that the development of behavioral sensitization to cocaine is mediated by alterations in the mesolimbic dopamine pathway.

II. Antagonists Effects:

As discussed previously, it has generally been assumed that the development of behavioral sensitization to cocaine requires the repeated intermittent stimulation of dopamine receptors (Henry & White, 1991; Kalivas & Stewart, 1991; Robinson & Becker, 1986; Robinson & Berridge, 1993). Consistent with this view, repeated

cocaine treatments have been shown to result in a transient subsensitivity of dopamine D2-type autoreceptors, and a long-lasting increase in the sensitivity of dopamine D1-type receptors (Henry & White,1991; White, 1996). These changes have been proposed to mediate the development of behavioral sensitization to cocaine and to occur as a result of the cocaine-induced increase in extracellular dopamine (Kalivas & Stewart, 1991; Robinson & Becker, 1986). This hypothesis would predict, however, that concurrent treatment with dopamine antagonists would block the development of behavioral sensitization to cocaine. Clearly, the present results are inconsistent with this view.

In the present experiment, rats were pretreated with a combination of the selective D1-type antagonist, SCH 23390, and the selective D2-type antagonist, eticlopride prior to each daily cocaine treatment. This combined treatment greatly suppressed all indices of locomotor activity and completely blocked the locomotor-activating effects of cocaine. Thus, there appears to be no question that this drug cocktail effectively blocked dopamine receptors. Despite this antagonism, however, rats pretreated with the antagonist combination and cocaine were clearly supersensitive to the cocaine challenge injection. Thus, blocking both D1- and D2-type receptors did not block the development of sensitization to cocaine.

This finding is consistent with previous work from our laboratory, which indicated that the selective D1- and D2-type dopamine antagonists administered alone are ineffective in preventing the development of cocaine-induced behavioral

sensitization (Mattingly et al., 1994; Mattingly et al., 1996). Other researchers have also failed to prevent the development of behavioral sensitization to cocaine using other selective dopamine antagonists with mice (Kuribara & Uchihashi, 1993). Moreover, this antagonist combination was recently shown to be ineffective in blocking the development of cocaine-induced behavioral sensitization in a study using a non-associative procedure and longer withdrawal intervals (White et al., 1998). Taken together, these findings suggest that the development of behavioral sensitization to cocaine does not require the repeated stimulation of dopamine receptors.

Curiously, it has been reported that concurrent treatments with high doses of the relatively non-selective dopamine antagonist, haloperidol, does block the development of cocaine-induced behavioral sensitization using a procedure similar to that used in the current study (Mattingly et al., 1996). Moreover, haloperidol has been reported to block the development of sensitization to cocaine using a novel one-exposure treatment paradigm (Weiss, Post, Pert, Woodward, & Murman, 1989). As noted earlier, since very high doses of haloperidol were used in these studies, it was assumed that haloperidol was effective because of a combined blockade of both D1- and D2-type receptors (cf., Mattingly et al., 1996). However, the current results are inconsistent with this interpretation. At present, the mechanisms mediating the effectiveness of haloperidol in blocking the development of sensitization to cocaine are unclear. Nonetheless, besides blocking dopamine receptors, haloperidol also has antagonistic actions at serotonergic receptors and has a high affinity for sigma

receptors (O'Dell et al., 1990; Quiron et al., 1992). Thus, these non-dopaminergic effects of haloperidol may be involved in some way in the development of behavioral sensitization to cocaine. Indeed, cocaine is a potent inhibitor of serotonin re-uptake and alteration in the serotonergic neurotransmitter system have been reported following repeated cocaine administration (Ritz, Cone & Kuhar, 1990).

III. Antagonist-Induced Sensitivity to Cocaine:

As discussed previously, selective dopamine D1-type receptor antagonists have been reported to block the development of sensitization to other dopamine agonists such as apomorphine, amphetamine, bromocriptine, and quinpirole (Drew & Glick, 1990; Mattingly et al., 1991; Mattingly et al., 1993; Wise & Carlezon, 1994). Thus, the inability of D1-type antagonists to block cocaine-induced sensitization was unexpected since most researchers have assumed that sensitization to these drugs involved a common dopaminergic mechanism. Another intriguing finding of the present study is the increased sensitivity to cocaine observed in animals that were pretreated with only the antagonist combination (cf., Figure 8.). A similar antagonist-induced increase in subsequent sensitivity to cocaine has recently been observed following brief repeated treatments with haloperidol, SCH 23390, sulpiride, and YM-09151-2 (Kuribara & Uchihashi, 1993; Mattingly et al., 1994; White, 1998). Moreover, repeated treatments with the mixed dopamine antagonist cis-(Z)-flupentixol, has been reported to increase subsequent sensitivity to cocaine in a self-

administration paradigm (Peltier & Emmett-Oglesby, 1994). Thus, brief treatments with dopamine antagonists appear to enhance sensitivity to both the locomotor-activating and the rewarding effects of cocaine. These findings are surprising because repeated dopamine antagonist treatments do not increase subsequent sensitivity to other dopamine agonists (Mattingly et al., 1991; Stewart & Vezina, 1989; Vezina & Stewart, 1989). Taken together, these findings also suggest that the development of sensitization to cocaine may involve a unique neurochemical mechanism.

At present, the neurochemical mechanism mediating this antagonist-induced increase in sensitivity to cocaine is unclear. Although changes in dopamine receptors may be involved, antagonist-induced dopamine receptor up-regulation is usually found only after several weeks of antagonist treatments (Creese & Chen, 1985; Hess, Albers, Le & Creese, 1986). Moreover, as noted above, the locomotor-activating effects of the direct dopamine agonist, apomorphine, are not enhanced after similar antagonist treatments (Mattingly et al., 1991). Despite the lack of observable morphological changes in dopamine receptors, some recent evidence suggests brief antagonist treatments might produce some functional changes in dopamine receptors (White et al., 1998). For example, after brief treatments with the selective dopamine D1-type antagonist SCH 23390, neurons with dopamine receptors in the nucleus accumbens display an augmented electrophysiological response to dopamine (White et al., 1998). Although the basis for this increased responsiveness is unknown, it could play a role in

the antagonist-induced increase in behavioral sensitivity to cocaine. Clearly, additional research is warranted to determine the exact basis for this effect.

IV. Summary and Conclusions:

The present results clearly indicate that behavioral sensitization develops to cocaine after brief treatments. More important, the current findings indicate that the development of sensitization to cocaine is not prevented by concurrently blocking both D1-type and D2-type dopamine receptors. This finding suggests that other neurochemical systems, besides dopaminergic, may be involved in the development of sensitization to cocaine. Since sensitization to other psychostimulant drugs such as amphetamine and apomorphine can be prevented with concurrent treatments with mixed and selective D1-type dopamine antagonists, the current findings suggest that cocaine-induced behavioral sensitization may be mediated by unique neurochemical mechanisms. Moreover, the current results indicate that brief treatments with dopamine antagonists alone increase subsequent sensitivity to cocaine. This finding also contrasts with sensitization studies with other dopamine agonists, and further suggests that the mechanisms mediating cocaine-induced behavioral sensitization differ from those of other psychostimulant drugs.

The current results may have significant implications for the treatment of drug abuse. As noted previously, one of the main factors underlying the high relapse rate among cocaine abusers in withdrawal is the intense and persistent craving (cf.,

Robinson & Berridge, 1993). Like sensitization, craving is known to increase in intensity and persistence with repeated drug exposure. Thus, drugs are needed for treatment which will block or reverse craving, and which are not reinforcing when administered alone. Moreover, the ideal drug will also decrease subsequent sensitivity to cocaine. Assuming that behavioral sensitization is a valid model of craving, the present results suggest that the use of dopamine antagonists would be an ineffective treatment for cocaine addiction. First, these agents do not block the development of behavioral sensitization, and therefore, according to the model, would not prevent the further development of craving if taken concurrently with cocaine. More important, since these drugs increase subsequent sensitivity to cocaine, repeated treatments with these agents during withdrawal may actually increase craving in the absence of the drug. Clearly, additional research is necessary to help define precisely the neurochemical alterations induced by repeated cocaine exposure before the appropriate drug treatments can be developed.

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APPENDIX A

ANOVA SUMMARY TABLES

Table 2

Summary of Analysis of Variance Performed on Mean Distance Traveled : Pretreatment Days 1-4

Source	df	MS	F	nu^2
Between Groups				
Antagonist (A)	1	205683542	200.35***	.82
Cocaine (C)	1	85652845	83.43***	.65
AxC	1	84411477	82.22***	.65
Error	44	1026608		
Within Groups				
Day (D)	3	354268.4	0.63	
AxD	3	371565.9	0.66	
CxD	3	944127.9	1.67	
AxCxD	3	983614.0	1.74	
Error	132	564925		
Block (B)	3	21050114	219.12***	.83
AxB	3	21241682	221.12***	.83
CxB	3	5008374	52.14***	.54
AxCxB	3	5065515	52.73***	.55
Error	132	96065		
DxB	9	118099.2	1.76	
AxDxB	9	124595.9	1.85	
CxDxB	9	101167.1	1.50	
AxCxDxB	9	100432.1	1.49	
Error	396	67240		

***p .0001

Table 3

Summary of Analysis of Variance Performed on Mean Stereotypic Counts: Pretreatment Days 1-4

Source	df	MS	F	nu^2
Between Groups				
Antagonist (A)	1	753342610	489.21***	.92
Cocaine (C)	1	155356243	100.89***	.70
AxC	1	158001218	102.60***	.70
Error	44	1539925		
Within Groups				
Day (D)	3	1678052.1	1.97	
AxD	3	440395.7	0.52	
CxD	3	438940.7	0.52	
AxCxD	3	774374.1	0.91	
Error	132	850206		
Block (B)	3	29372554	168.19***	.79
AxB	3	26644924	152.57***	.78
CxB	3	1802043	10.32***	.19
AxCxB	3	1889990	10.82***	.20
Error	132	174641		
DxB	9	338584.5	3.30**	.07
AxDxB	9	370277.3	3.61**	.08
CxDxB	9	123611.8	1.21	
AxCxDxB	9	149978.7	1.46	
Error	396	102552		

***p .0001
**p .001

Table 4

Summary of Analysis of Variance Performed on Mean Number of Rears: Pretreatment Days 1-4

Source	df	MS	F	nu^2
Between Groups				
Antagonist (A)	1	787328.26	93.81***	.68
Cocaine (C)	1	242820.75	28.93***	.40
AxC	1	240196.26	28.62***	.39
Error	44	8392.77		
Within Groups				
Day (D)	3	298.8368	0.14	
AxD	3	246.1753	0.11	
CxD	3	2601.1910	1.21	
AxCxD	3	2726.5295	1.27	
Error	132	2148.44		
Block (B)	3	90489.89	138.03***	.76
AxB	3	90921.55	138.69***	.76
CxB	3	9440.20	14.40***	.25
AxCxB	3	9575.41	14.61***	.25
Error	132	655.58		
DxB	9	1019.410	1.13	
AxDxB	9	1032.290	1.14	
CxDxB	9	1463.616	1.62	
AxCxDxB	9	1484.857	1.64	
Error	396	905.59		

***p .0001

Table 5

Summary of Analysis of Variance Performed on Mean Distance Traveled: Cocaine Challenge Day 5

Source	df	MS	F	nu^2
Between Groups				
Antagonist (A)	1	18530931	14.66**	.25
Cocaine (C)	1	15357533	12.15**	.22
AxC	1	65300	0.05	
Error	44	1264380		
Within Groups				
Block (B)	3	37232750	199.30***	.82
AxB	3	262863	1.41	
CxB	3	1654038	8.85***	.17
AxCxB	3	100198	0.54	
Error	132	186814		

***p .0001
**p .001

Table 6

Summary of Analysis of Variance Performed on Mean Stereotypic Count: Cocaine Challenge Day 5

Source	df	MS	F	nu^2
Between Groups				
Antagonist (A)	1	18396061	16.69***	.28
Cocaine (C)	1	1122867	1.02	
AxC	1	469360	0.43	
Error	44	1102296		
Within Groups				
Block (B)	3	21520558	114.09***	.72
AxB	3	1866240	9.89***	.18
CxB	3	168431	0.89	
AxCxB	3	118972	0.63	
Error	132	188628		

***p .0001

Table 7

Summary of Analysis of Variance Performed on Mean Number of Rears: Cocaine Challenge Day 5

Source	df	MS	F	nu^2
Between Groups				
Antagonist (A)	1	87680.255	16.86**	.28
Cocaine (C)	1	13685.630	2.63	
AxC	1	1349.380	0.26	
Error	44	5201.75		
Within Groups				
Block (B)	3	93620.96	102.24***	.70
AxB	3	4128.13	4.51*	.09
CxB	3	7051.92	7.70***	.15
AxCxB	3	904.12	0.99	
Error	132	915.70		

***p .0001
**p .001
*p .01

APPENDIX B

COUNTERBALANCING

TABLE 8

COUNTERBALANCING

Squad #	Subject #	Pretreatment Group	Chamber #
1	1	Vehicle-Vehicle	1
1	2	Vehicle-Cocaine	2
1	3	SCH/Etic-Vehicle	3
1	4	SCH/Etic-Cocaine	4
2	5	SCH/Etic-Vehicle	1
2	6	SCH/Etic-Cocaine	2
2	7	Vehicle-Vehicle	3
2	8	Vehicle-Cocaine	4
3	9	Vehicle-Cocaine	1
3	10	Vehicle-Vehicle	2
3	11	SCH/Etic-Cocaine	3
3	12	SCH/Etic-Vehicle	4
4	13	SCH/Etic-Cocaine	1
4	14	SCH/Etic-Vehicle	2
4	15	Vehicle-Cocaine	3
4	16	Vehicle-Vehicle	4
5	17	Vehicle-Vehicle	1
5	18	Vehicle-Cocaine	2
5	19	SCH/Etic-Vehicle	3
5	20	SCH/Etic-Cocaine	4
6	21	SCH/Etic-Vehicle	1
6	22	SCH/Etic-Cocaine	2
6	23	Vehicle-Vehicle	3
6	24	Vehicle-Cocaine	4
7	25	Vehicle-Cocaine	1
7	26	Vehicle-Vehicle	2
7	27	SCH/Etic-Cocaine	3
7	28	SCH/Etic-Vehicle	4
8	29	SCH/Etic-Cocaine	1
8	30	SCH/Etic-Vehicle	2
8	31	Vehicle-Cocaine	3
8	32	Vehicle-Vehicle	4
9	33	Vehicle-Vehicle	1
9	34	Vehicle-Cocaine	2
9	35	SCH/Etic-Vehicle	3
9	36	SCH/Etic-Cocaine	4

TABLE 8 (Continued)

Squad #	Subject #	Pretreatment Group	Chamber #
10	37	SCH/Etic-Vehicle	1
10	38	SCH/Etic-Cocaine	2
10	39	Vehicle-Vehicle	3
10	40	Vehicle-Cocaine	4
11	41	Vehicle-Cocaine	1
11	42	Vehicle-Vehicle	2
11	43	SCH/Etic-Cocaine	3
11	44	SCH/Etic-Vehicle	4
12	45	SCH/Etic-Cocaine	1
12	46	SCH/Etic-Vehicle	2
12	47	Vehicle-Cocaine	3
12	48	Vehicle-Vehicle	4